

# World Journal of *Hypertension*

*World J Hypertens* 2018 October 21; 8(1): 1-4



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# World Journal of Hypertension

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Volume 8 Number 1 October 21, 2018

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**NAME OF JOURNAL**

*World Journal of Hypertension*

**ISSN**

ISSN 2220-3168 (online)

**LAUNCH DATE**

December 23, 2011

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**PUBLICATION DATE**

October 21, 2018

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## Blood pressure goals: A moving target

Nitin Thinda, Steven Tringali, Jian Huang

Nitin Thinda, Steven Tringali, Jian Huang, Department of Medicine, University of California San Francisco-Fresno Medical Education Program, Fresno, CA 93701, United States

Jian Huang, Department of Medicine Service, VA Central California Health Care System, Fresno, CA 93703, United States

ORCID Number: Jian Huang (0000-0002-7436-6756).

Author contributions: All the authors contributed to this manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest for this article.

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Manuscript source: Invited Manuscript

Correspondence to: Jian Huang, FACP, MD, Professor, Staff Physician, Department of Medicine Service, VA Central California Health Care System, 2615 E Clinton Ave, Fresno, CA 93703, United States. [jian.huang@va.gov](mailto:jian.huang@va.gov)  
Telephone: +1-559-2256100  
Fax: +1-559-2416484

Received: August 1, 2018

Peer-review started: August 1, 2018

First decision: August 20, 2018

Revised: August 25, 2018

Accepted: October 12, 2018

Article in press: October 13, 2018

Published online: October 21, 2018

### Abstract

Clinical guidelines on hypertension have evolved over

the past several decades. Each recommends varying blood pressure (BP) cut-offs which define hypertension, determine the thresholds to initiate pharmacotherapy, and guide treatment targets. In addition, different techniques of measuring BP in clinical trials may further contribute to the discrepancies in the achieved BP targets. Physicians find it difficult to navigate through different recommendations for hypertension management based on studies among different age groups and patients with a variety of co-morbidities and target organ involvement. In 2003, JNC 7 recommended a BP goal of < 140/90 mmHg in the general population and < 130/80 mmHg in those with diabetes mellitus or renal disease. JNC 8 re-set the BP target at < 140/90 mmHg for all adults under the age of 60 regardless of co-morbidities, and an even higher target of < 150/90 mmHg for those 60 years or older without diabetes or chronic kidney disease. The more recent results of the Systolic BP Intervention Trial (SPRINT) have a significant influence on the 2017 American College of Cardiology (ACC) and American Heart Association (AHA) guideline which redefines hypertension as BP  $\geq$  130/80 mmHg. It emphasizes individualized cardiovascular risk assessment and recommends a more aggressive BP target of < 130/80 mmHg and a treatment threshold based on the age, co-morbidities, and cardiovascular risk. The 2017 ACC/AHA guideline also advocates proper BP measurement and provides the estimates of corresponding BP values for clinic, home, and ambulatory BP monitoring measurements. A higher prevalence of hypertension is expected based on the ACC/AHA 2017 guideline. Its implementation may potentially lead to better BP control through enhanced awareness, improved adherence, and more timely initiation and intensification of pharmacologic therapy. Although there is no one-size-fits-all BP target, the ACC/AHA 2017 guideline is simple, inclusive and practical. Nonetheless, more studies are warranted to help further individualize BP goals for elderly patients and those with certain co-morbidities or multiple cardiovascular risk factors.

**Key words:** Hypertension; Blood pressure; Hypertension guidelines; Blood pressure goals

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**Core tip:** The most recent 2017 American College of Cardiology and American Heart Association guideline redefines hypertension as blood pressure (BP)  $\geq 130/80$  mmHg. It recommends initiation of pharmacotherapy for all adults with BP  $\geq 140/90$  mmHg and for patients with BP  $\geq 130/80$  mmHg who are  $\geq 65$ , have diabetes, chronic kidney disease, cardiovascular disease (CVD), or a 10-year CVD risk of  $\geq 10\%$ . Although optimal BP varies individually, it seems reasonable to recommend a BP goal of  $< 130/80$  mmHg, and age/risk-stratified pharmacotherapy threshold. More clinical data are needed to further individualize BP goals for elderly patients and those with certain co-morbidities or multiple cardiovascular risks.

Thinda N, Tringali S, Huang J. Blood pressure goals: A moving target. *World J Hypertens* 2018; 8(1): 1-4 Available from: URL: <http://www.wjgnet.com/2220-3168/full/v8/i1/1.htm> DOI: <http://dx.doi.org/10.5494/wjh.v8.i1.1>

Hypertension affects more than 100 million United States adults and its prevalence increases with age<sup>[1]</sup>. It remains one of the most common primary diagnoses for adult office visits<sup>[2]</sup> and is a major modifiable risk factor for cardiovascular disease (CVD) and premature mortality<sup>[3]</sup>. Antihypertensive therapy reduces risk of CVD and all-cause mortality<sup>[4]</sup>. Clinical guidelines on high blood pressure (BP) have evolved over the past several decades since clinical evidence of therapeutic benefits became available in treating elevated diastolic BP from 2-phase VA co-operative study completed in early 1970's and later in lowering systolic BP from SHEP study published in 1991. These clinical practice guidelines recommend varying BP cut-offs which define hypertension, determine the thresholds to initiate pharmacotherapy and guide treatment targets. Despite more available data from recent outcome-based clinical trials, physicians still find it difficult to navigate through different recommendations for the management of hypertension based on studies among different age groups and patients with a variety of co-morbidities and target organ involvement. In addition, different techniques of measuring BP in these trials may further contribute to the discrepancies in the achieved BP targets<sup>[5]</sup>.

Over the past 15 years, the therapeutic BP target has been changed significantly. In 2017, the American College of Cardiology (ACC) and American Heart Association (AHA) along with 9 additional partners published a new hypertension guideline<sup>[6]</sup>. This guideline is intended to be a comprehensive yet succinct resource that aids physicians in managing hypertension and is an update of the Seventh Report of the Joint National

Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) which was published in 2003<sup>[7]</sup>. JNC 7 recommended a BP goal of  $< 140/90$  mmHg in the general population and  $< 130/80$  mmHg in those with diabetes mellitus (DM) or chronic kidney disease (CKD). It took a total of 11 years before the Eighth Joint National Committee (JNC 8) released an update<sup>[8]</sup>. In 2014, JNC 8 recommended the BP goal of  $< 140/90$  mmHg for adults with DM, CKD, and those under the age of 60, and an even higher target of  $< 150/90$  mmHg for adults 60 years or older without DM or CKD. The JNC 8 recommendations were based on a systematic review restricted to evidence from randomized control trials (RCTs). Although all studies included had their merits, they also had their limitations. For example, the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) was only powered to detect a 40% relative risk reduction in the primary endpoint and it followed patients for only two years<sup>[9]</sup>. The Valsartan in Elderly Isolated Systolic Hypertension (VALISH) trial was significantly underpowered with fewer primary endpoint events than predicted<sup>[10]</sup>. The Hypertension in the Very Elderly Trial (HYVET) was stopped early for mortality benefit with an achieved average systolic BP of 144 mmHg. This provided evidence for the BP target of  $< 150/90$  mmHg in those  $> 80$  years. However, it cannot be determined whether further reduction of systolic BP to a lower target would benefit this age group<sup>[11]</sup>. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial in diabetic patients showed no significant difference in the primary outcome when comparing target systolic BP  $< 140$  mmHg vs  $< 120$  mmHg. However, the event rate in the control group was lower than expected. In addition, there were more adverse events in the intensive treatment group. The study was criticized for being underpowered as well<sup>[12]</sup>.

After the publication of JNC 8, the results of the Systolic Blood Pressure Intervention Trial (SPRINT)<sup>[5]</sup> were released in 2015 which have a significant influence on the 2017 ACC/AHA guideline<sup>[6]</sup>. SPRINT was conducted among high-risk hypertensive patients with CKD, clinical or sub-clinical CVD or Framingham score for 10-year CVD risk  $\geq 15\%$  but without diabetes and prior stroke. It showed a significantly lower rate of primary composite outcome and all-cause death with the intensive treatment to target systolic BP  $< 120$  mmHg compared to the standard therapy with systolic BP goal of  $< 140$  mmHg. The study findings led to its early cessation after a median follow up of 3.26 years. Like all other studies, SPRINT too had its share of critics. Participants were exclusively non-diabetic. BP readings were based on an average of 3 fully automated and unattended measurements which are lower compared with BP values in most other clinical trials. This makes it very difficult to standardize BP measurements during routine office visits and to translate clinical guidelines into daily practice. Existing evidence suggests an alternative extrapolation by adding approximately

10-12 mmHg to the SBP achieved in SPRINT trial as an equivalent office BP reading<sup>[13]</sup>. The early termination of SPRINT may have overestimated the magnitude of benefit. The reduction of its primary composite outcome with intensive treatment was driven mainly by heart failure and CVD mortality, not myocardial infarction or stroke. There was also a concern of marked increase in some adverse events such as hypotension, syncope, electrolyte imbalances, and acute kidney injury in the intensive therapy group. Observational clinical data have suggested an increased risk with excessive BP lowering for certain CVD outcomes and within specific populations. The beneficial effects of BP control can be lost or reversed in certain hypertensive subgroups when BP levels are reduced below physiologic limits. This was referred to as J-curve phenomenon, since there should be a physiologic nadir for BP cut-offs below which the risk of cardiovascular events increases<sup>[14]</sup>. Different co-morbidities may have different nadirs of the J-curve. Thus, optimizing BP for stroke prevention may not reduce risk of cardiac, renal or retinal events and may even increase risk of serious adverse events<sup>[15]</sup>. Therefore, BP targets ultimately should be a balance between risks and benefits.

The 2017 ACC/AHA guideline redefines hypertension as systolic BP  $\geq$  130 mmHg or diastolic BP  $\geq$  80 mmHg and recommends initiation of pharmacotherapy for all adults with BP  $\geq$  140/90 mmHg and for patients with BP  $\geq$  130/80 mmHg who are 65 years or older, have DM, CKD, CVD, or a 10-year CVD risk of  $\geq$  10%<sup>[6]</sup>. Though the new guideline is not perfect, and optimal BP will differ from individual to individual, it is important to note that the goal of < 130/80 mmHg is notably higher than that for the intensive therapy in SPRINT, and it does help set pharmacotherapy threshold based on the age, co-morbidities, and CV risk. Individualized CV risk stratification to guide decision making with an emphasis on risk reduction is more reasonable for those with multiple co-morbidities and high CV risk<sup>[6]</sup>.

Proper BP measurement is critical in making the treatment decision, since the new guideline recommends both lower thresholds and a lower target. Average BP levels based on  $\geq$  2 readings obtained on  $\geq$  2 occasions during office visits should be used for the initial evaluation. Out-of-office and self-monitoring of BP measurements are recommended to confirm the diagnosis and to titrate BP medications. The 2017 ACC/AHA guideline provides the estimates of corresponding BP values for clinic, home BP monitoring (HBPM), daytime, nighttime, and 24-h ambulatory BP monitoring measurements<sup>[6]</sup>.

BP targets that do not discriminate between general populations, the elderly, and the very elderly, could be problematic because isolated systolic hypertension affects many patients older than 70 years. More aggressive treatment targeting the systolic BP in the elderly without consideration of diastolic BP may cause harm. Evidence from RCTs to recommend diastolic BP target is lacking. Existing literature suggests that lower-

ing diastolic BP to below 60-80 mmHg is associated with adverse clinical outcomes among high-risk patients<sup>[16]</sup>.

A higher prevalence of hypertension is expected based on the ACC/AHA 2017 guideline<sup>[1]</sup>. Its implementation may potentially lead to better BP control through more attention to hypertension, improved adherence to lifestyle modification, and, especially among those with increased risk for CVD, timely initiation and justified intensification of pharmacologic therapy.

Although there is no one-size-fits-all BP target, the ACC/AHA 2017 guideline is simple, inclusive and practical. Nonetheless, more studies are warranted to help further individualize blood pressure goals for patients who may be elderly or have other co-morbidities such as DM, CKD, CAD, history of stroke, or multiple CV risk factors. It is with more clinical studies designed to address these questions that we hope to finally be able to home in the moving BP target.

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